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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/535,630	11/04/2005	Gerhard Hoefle	930008-2200	9251

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EXAMINER	
MABRY, JOHN	

ART UNIT	PAPER NUMBER
1625	

MAIL DATE	DELIVERY MODE
12/22/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/535,630	HOEFLE ET AL.	
	Examiner	Art Unit	
	JOHN MABRY	1625	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 October 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-72* is/are pending in the application.

4a) Of the above claim(s) *3-67* is/are withdrawn from consideration.

5)☒ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2 and 68-72* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *5/20/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicant has submitted an IDS dated May 20, 2005 but has not provided references therein. Examiner attained listed references in IDS and they have been considered.

Examiner's Response

Applicant's response on October 20, 2008 filed in response to the Election/Restriction dated August 20, 2008 has been received and duly noted. The Examiner acknowledges Applicants' election of Group I without traverse. If compounds are found to be allowable, Applicant is entitled to rejoinder of a process of preparing compounds which contain all the limitations of Group I.

Thus, the restriction requirement is deemed proper and **FINAL**.

In view of this response, the status of the rejections/objections of record is as follows:

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 2, 68, 69 and 72 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Regarding claims, the phrase "preferably" and “especially” renders the claims indefinite because it is unclear whether the limitation(s) following the phrase are part of the claimed invention. See MPEP § 2173.05(d).

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-2 and 68-72 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for R10 being H, alkyl and OR9 where R9 is alkyl, R being H, alkyl or OH, and T being H, OR4 where R4=H, but does not reasonably provide enablement for R10 and T being the entire scope as claimed.

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims. The Specification does not provide any support for said variables at R10 position. The Specification describe starting materials and methods for synthesis of compounds wherein R10 being H, alkyl and OR9 where R9 is alkyl, R being H, alkyl or OH, and T being H, OR4 where R4=H, but does not describe or list any reagents wherein compounds can be used to synthesis compounds where R, R10 and T being the entire scope as claimed.

Pursuant to *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988), one considers the following factors to determine whether undue experimentation is required: (A) The breadth of the claims; (B) The nature of the invention; (C) The state of the prior art; (D) The level of one of ordinary skill; (E) The level of predictability in the art; (F) The amount of direction provided by the inventor; (G) The existence of working

examples; and (H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure. Some experimentation is not fatal; the issue is whether the amount of experimentation is "undue"; see *In re Vaeck*, 20 USPQ2d 1438, 1444.

The analysis is as follows:

Breadth of claims: Scope of the compounds. Owing to the range of many variables, of highly substituted Tubulysin compounds are embraced.

Level of predictability in the art: It is well established that "the scope of enablement varies inversely with the degree of unpredictability of the factors involved," and chemical reactivity (which is affected by determinants such as substituent effects, steric effects, bonding, molecular geometry, etc) is generally considered to be an unpredictable factor. See *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970).

Direction or Guidance: That provided is very limited. Applicant shows a general synthesis of compounds of application's general formula I. The Specification describes starting materials and methods for synthesis of compounds wherein R being H, alkyl or OH; R10 being H, alkyl and OR9 where R9 is alkyl and T being H, OR4 where R4=OH, but does not describe or list any reagents wherein compounds can be used to synthesis compounds where R10 and T being the entire scope as claimed. There is limited evidence in the Specification of the example compounds that only covers no or a small portion of the substituents claimed of formula. Thus, there is no specific direction or

guidance regarding said compounds specifically mentioned in Scope.

The availability of the starting material that is needed to prepare the invention as claimed is at issue here…As per MPEP 2164.01 (b). A key issue that can arise when determining whether the specification is enabling is whether the starting materials or apparatus necessary to a make the invention are available. In the biotechnical area, this is often true when the product or process requires a particular strain of microorganism and when the microorganism is available only after extensive screening. The Court *in re Ghiron*, 442 F.2d 985, 991, 169 USPQ 723, 727 (CCPA 1971), made it clear that if the practice of a method requires a particular apparatus, the application must provide a sufficient disclosure of the apparatus if the apparatus is not readily available. The same can be said if certain chemicals are required to make a compound or practice a chemical process. *In re Howarth*, 654 F.2d 103, 105, 210 USPQ 689, 691 (CCPA 1981).

State of the Prior Art: These compounds are substituted Tubulysin compounds as claimed are well documented in the art as stated in art rejections below.

It is not trivial to experimentally interchange any and all of the many substituents that exist. As generally described by F. Zaragoza Dörwald, most organic syntheses fail initially and chemical research is highly inefficient due to chemists spending most of their time "finding out what went wrong and why". Therefore, most syntheses of organic

compounds are labor-intensive and demanding. Additionally, most final synthetic routes to desired organic molecules are usually very different from initially planned routes. A highly skilled chemist can agree that for many successful organic compounds made, many failures are encountered and experimental repetition is common. This also contributes to the burden and unpredictability of the syntheses of said compounds. (see "Side Reactions in Organic Synthesis: A Guide to Successful Synthesis Design" 2005 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim.

Working Examples: Applicant shows examples where R being H, alkyl or OH, X=H and CH2OC(O)alkyl and T being H, OR4 where R4=OH, but no working examples were shown wherein R, R10 and T equal aforementioned substituents have been made or used of any kind by Applicant.

Skill of those in the art: The ordinary artisan is highly skilled, e.g. a masters or PhD level chemist.

The quantity of experimentation needed: Since there are very limited working examples as described above, the amount of experimentation is expected to be high and burdensome.

Due to the level of unpredictability in the art, the very limited guidance provide, and the lack of working examples, the Applicant has not provided sufficient guidance for the artisan to make the invention.

MPEP 2164.01(a) states, "A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the

application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. *In re Wright*, 999 F.2d 1557,1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)." That conclusion is clearly justified here.

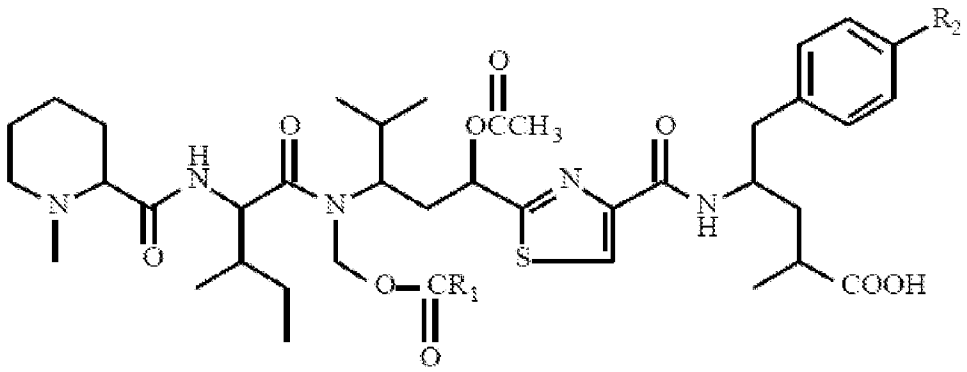
Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 68 and 72 are rejected under 35 U.S.C. 102(a) as being anticipated by Hamel et al (Curr. Med. Chem. – Anti-Cancer Agents, 2002, Vol. 2, No. 1).

Hamel discusses compounds of Formula I where Y=electron pair, Z=CH3, X=CH2)OC(O)alkyl, W=H, V=OC(O)CH3, R=OH, U and S=H and T=OH (see Fig.(14), page 42 and as shown below).

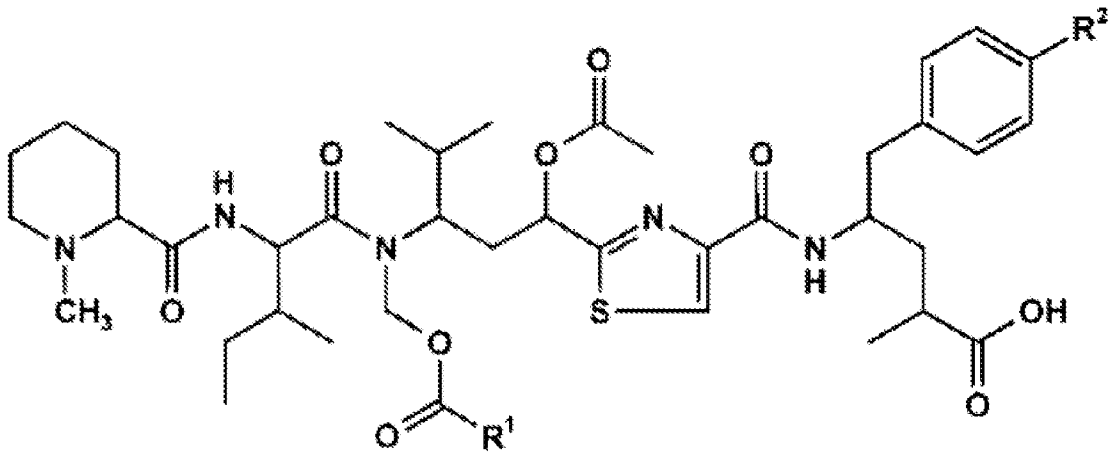


Tubulysins

	R_1	R_2
A	$CH_2CH(CH_3)_2$	OH
B	$CH_2CH_2CH_3$	OH
C	CH_2CH_3	OH
D	$CH_2CH(CH_3)_2$	H
E	$CH_2CH_2CH_3$	H
F	CH_2CH_3	H

Claims 1, 68 and 72 are rejected under 35 U.S.C. 102(b) as being anticipated by Sasse et al (Journal of Antibiotics 2000, 53, 879-885).

Sasse discusses compounds of Formula I where Y=electron pair, Z=CH3, X=CH2)OC(O)alkyl, W=H, V=OC(O)CH3, R=OH, U and S=H and T=H, OH (see Fig. 1, page 880).



Tubulysin A $R^1 = CH_2\text{-}CH(CH_3)_2$; $R^2 = OH$

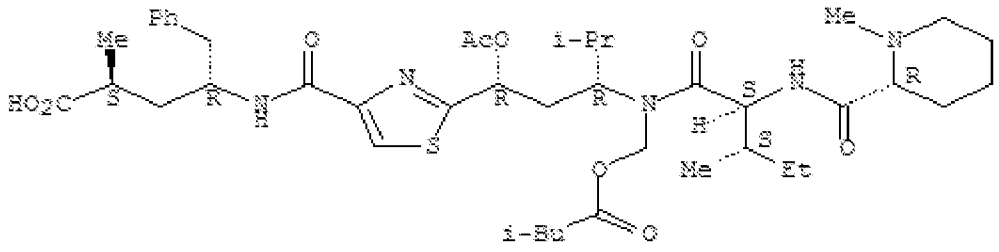
Tubulysin B $R^1 = CH_2\text{-}CH_2\text{-}CH_3$; $R^2 = OH$

Tubulysin D $R^1 = CH_2\text{-}CH(CH_3)_2$; $R^2 = H$

Tubulysin E $R^1 = CH_2\text{-}CH_2\text{-}CH_3$; $R^2 = H$

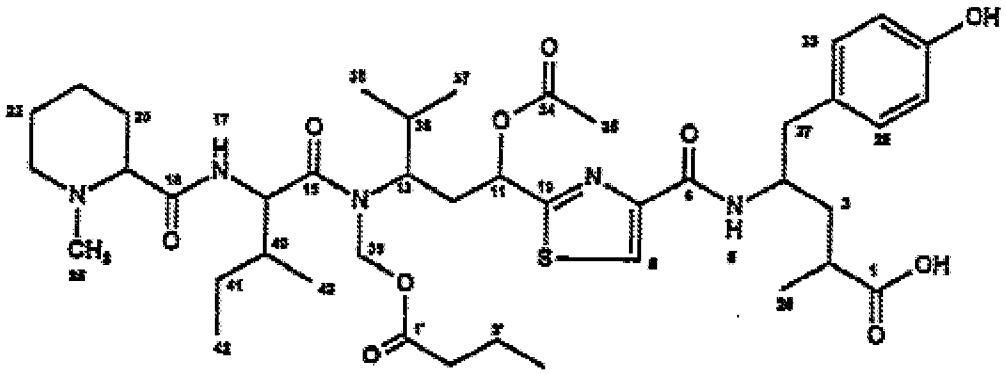
Claims 1, 68 and 72 are rejected under 35 U.S.C. 102(b) as being anticipated by Hoefle et al (DE 10008089 A1) (PTO-1449).

DE ‘089 discusses compounds of Formula I where Y=electron pair, Z=CH3, X=CH2)OC(O)alkyl, W=H, V=OC(O)CH3, R=OH, U and S=H and T=H (see compound 1, page 6 and claim 1).



Claims 1, 68 and 72 are rejected under 35 U.S.C. 102(b) as being anticipated by Hoefle et al (DE 19638870 A1) (PTO-1449).

DE '870 discusses compounds of Formula I where Y=electron pair, Z=CH3, X=CH2)OC(O)alkyl, W=H, V=OC(O)CH3, R=OH, U and S=H and T=H (see compounds on page 2 and claims 1-2 and Figures 1-3).



Conclusion

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to John Mabry, PhD whose telephone number is (571) 270-1967. The examiner can normally be reached on M-F from 9am to 5pm.

If attempts to reach the examiner by telephone are unsuccessful, the Examiner's primary examiner can be reached at (571) 272-0684, first, or the Examiner's supervisor, Janet Andres, PhD, can be reached at (571) 272-0867. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

/John Mabry/
Examiner
Art Unit 1625

/Rita J. Desai/
Primary Examiner, Art Unit 1625